Host Susceptibility Branch Mission

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Mission Statement

To develop and test genetically modified and diverse animal models to determine (a) the range of their biological responses to toxic agents of public health importance, (b) the genetic and epigenetic bases for these biological responses, and (c) the mode or mechanistic basis for agent-specific toxicity in order to improve extrapolation across species.

Aims

The primary aim of research carried out by the Host Susceptibility Branch (HSB) is to develop new laboratory models and testing protocols for hazard identification and risk assessment. The models are intended to quantitatively capture the range of response between individuals that correlate with individual human susceptibility to toxicity and disease. Individual genetic differences harbored within the human population are believed to be the basis for individual susceptibility to environmental stressors that cause toxicity, including idiosyncratic drug toxicities. The goal of the HSB is to model this genetic diversity in the human population using genetically diverse laboratory animals for *in vivo* and *in vitro* toxicology studies.

These new tools will aid genetic analysis (meiotic mapping, haplotype association mapping, etc.) and identification of quantitative trait loci (QTL) for functional validation of the candidate genes that explain the variations in response to chemical exposure and disease between different individuals. By doing so, the HSB aims to identify the key genetic and epigenetic variations and pathways that modify or influence an individual's response — and, thus, the variance observed within a population of individuals — to chemical exposures of presumed or known risk to humans.

The results obtained will also provide clues for epidemiologic research or corroboration of epidemiology findings in animal models under defined exposure conditions, life stages, etc. Translational research based on identification of individuals susceptible to exposure-related disease may lead to the development of strategies and/or policies for prevention or reduction in exposure or, if necessary, development of therapies to mitigate the effects of exposure related diseases.

The investment of resources and the multidisciplinary expertise required to establish a new toxicology research strategy based upon the integration of toxicology and genetics

is significant. Novel and innovative research ideas and approaches are also required to make the most effective use of limited resources. Effective use of these resources would be enhanced by development of NIH intramural and extramural research collaborations. To capitalize on the rapidly developing knowledge base in academia, industry, and government, collaborative research partnerships are desired. The NTP HSB research and testing model is being developed to meet both NTP programmatic goals (nominations, model development, etc.) and to assist collaborating research groups in accomplishing common goals.

Research tasks that could be supported by HSB scientists and resources include, but are not limited to:

- Animal model selection
- Selection of toxicants of public health importance
- Acquisition of test agents
- Absorption, distribution, metabolism, and excretion (ADME) studies in multiple mouse inbred strains or genetically-modified mouse models
- Selection of dose and dose schedule for agent-specific environmental exposures
- Selection and determination of quantitative variants of toxicity (phenotyping) in selected models
- Development of experimental design protocols for large-scale toxicity and carcinogenicity research, biomarkers of exposure and effect, transcript expression arrays, and clinical and histopathology
- Statistical haplotype and toxicity phenotype association mapping analysis to identify causally related genes for functional genomic investigation and validation

NTP HSB programmatic research is conducted to develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals. The HSB research and testing mission enables the development of new research tools and approaches that generates data that strengthen scientific knowledge about potentially hazardous substances that supports the translation of promising discoveries in public health research for the public good.